The Rate of Reduction of *cis*-, *cis*-, *trans*-$[Pt^{IV}(NH_2Pr^i)_2Cl_2(OH)_2]$, CHIP, the Anti-cancer Drug by Ascorbic Acid

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Abstract

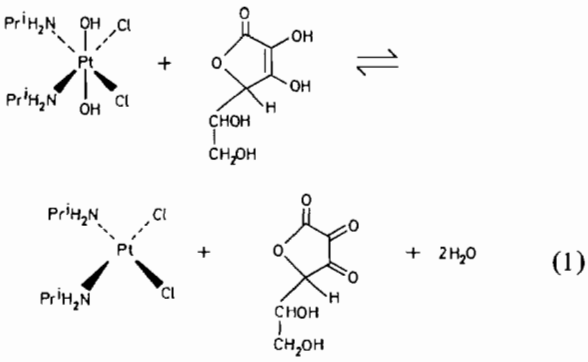
cis,cis,trans-$[Pt^{IV}(NH_3)_2Cl_2(OH)_2]$ reacts reversibly with ascorbic acid to give dehydroascorbic acid and mainly *cis*-$[Pt^{II}(NH_2Pr^i)_2Cl_2]$. The parameters for the forward reaction are: $k_f = 0.584\ M^{-1}\ s^{-1}$ at 37.0 °C, $\Delta H_f^{\neq} = 108.6 \pm 6.4$ kJ mol^{-1} and $\Delta S_f^{\neq} = 101 \pm 22$ J K^{-1} mol^{-1}.

One of the second generation of platinum containing anti-cancer drugs is CHIP, *cis,cis,trans*-$[Pt^{IV}(NH_2Pr^i)_2Cl_2(OH)_2]$. Unlike its forebear, *cis*-platin, *cis*-$[Pt^{II}(NH_3)_2Cl_2]$, its rate of reaction with nucleobases is very slow**. It has therefore been suggested that in order to become active CHIP is reduced *in vivo* to a platinum(II) state by reducing agents such as iron(II) or ascorbic acid [2]. We have confirmed that ascorbic acid does reduce CHIP and present the kinetics of the process here.

The rate of change of absorbance at λ320 nm was studied under pseudo first order conditions: [CHIP] = 3.12×10^{-4} M^{-1}, [ascorbic acid] = 3 to 12×10^{-3} M^{-1}. There is an initial reaction in which absorbance falls, followed by a second, very slow step in which absorbance increases gradually and is not complete after 30 h. The second step was not suitable for analysis. However the first reaction graphs of k_{obs} *versus* [ascorbic acid] were linear with finite intercepts, one interpretation of which is that the reaction is reversible. ^{1}H NMR evidence supports this supposition, *vide infra*. Kinetic parameters are k_f, 0.103 and 0.584 M^{-1} s^{-1} at 25.0 and 37.0 °C respectively; $\Delta H_f^{\neq}$, 108.6 ± 6.4 kJ mol^{-1}, $\Delta S_f^{\neq}$, 101 ± 22 J K^{-1} mol^{-1}; k_b, 0.78×10^{-3} and 2.46×10^{-3} s^{-1} at 25.0 and 37.0 °C respectively (f = forwards, b = backwards; the apparent first order rate constant, k_b, must be regarded as approximate since the back reaction is in fact second order, *vide infra*).

^{1}H NMR studies on ascorbic acid, dehydroascorbic acid, and on equimolar solutions of CHIP and ascorbic acid at $[1 \times 10^{-2}\ M^{-1}]$ in D_2O at ambient temperatures demonstrate that ascorbic acid is converted to dehydroascorbic acid, but that the reaction is not complete. (Resonances due to isopropyl groups are also present during the redox process. The ^{13}C NMR spectrum of the product mixture is complex. However it contains no resonances indicative of an organo–platinum bond as observed in various related platinum(II) 'ascorbate' complexes of 1,2-diaminocyclohexane [3]). *cis*-$[Pt(NH_2Pr^i)Cl_2]$ is not very soluble and is precipitated when the reaction between CHIP and ascorbic acid is carried out at concentrations of 0.01 M. As the yield of *cis*-$[Pt(NH_2Pr^i)_2Cl_2]$ is 50%, it is concluded that this is the main platinum containing product. The formation of this species is logical as it involves the least geometrical rearrangement of ligands around the platinum.

When one electron oxidising agent such as copper(II), iron(III) and VO^{2+} catalyse the oxidation of ascorbic acid, a radical is produced [4]. However the cleanness of the reaction here does not support a radical process. Instead a two-electron redox process is proposed as in eqn. (1) with the parameters given above.



(1)

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**For the reaction at 37.0 °C between CHIP and 5'-guanosinemonophosphoric acid at equimolar concentrations of 10^{-5} M, $t_{1/2} > 10^4$ h [1].

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References

1 S. S. Eapen and M. Green, unpublished work.
2 E. E. Blatter, J. F. Vallano, B. S. Krishman and J. C. Dabrowiak, *Biochemistry, 23,* 4817 (1984).
3 L. S. Hollis, A. R. Amundsen and E. W. Stern, *J. Am. Chem. Soc., 107,* 274 (1985).
4 M. M. Taqui Khan and A. E. Martell, 'Homogeneous Catalysis by Metal Complexes', Vol. I, Academic Press, New York/London, 1974, p. 114.